
**UNIVERSITI PUTRA MALAYSIA**

***PATHOGENESIS OF Corynebacterium pseudotuberculosis INFECTION AND VACCINATION TRIAL AGAINST CASEOUS LYMPHADENITIS IN GOATS***

**NUR ADZA RINA BINTI MOHD NORDI**

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# PATHOGENESIS OF *Corynebacterium pseudotuberculosis* INFECTION AND VACCINATION TRIAL AGAINST CASEOUS LYMPHADENITIS IN GOATS

By

**NUR ADZA RINA BINTI MOHD NORDI**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, In Fulfillments of the Requirements for the Degree of Doctor of Philosophy**

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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**November 2016**

**Chairman: Prof. Mohd Zamri Saad, PhD**
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*Corynebacterium pseudotuberculosis* is a Gram-positive bacterium that is responsible for a disease called caseous lymphadenitis (CLA) in goats and sheep. This disease has worldwide distributions and the bacterium can remain in the environment for months. It is difficult to eradicate and can be easily transmitted to naive animals. Furthermore, transmission and the pathology of the disease are not fully understood. Therefore, this experiment was conducted to determine the best route of infection of the disease, the clinical and pathological changes in goats following experimental infection, the humoral immune response via antibody titers shown by the infected goats, and the efficacy of a commercial vaccine in preventing CLA in goats in Malaysia.

Twenty adult healthy goats were selected and divided into 4 groups. All goats of the first 3 groups were infected with $10^7$ cfu/mL of live *C. pseudotuberculosis* via three different routes; the intradermal, the intranasal and the oral routes. The last group served as the uninfected control group. The goats were observed daily for clinical signs related to CLA for 30 days experimental period. Rectal temperatures and blood samples were taken periodically. The infected goats from all infected groups were depressed, showed lack of appetite, and increased in body temperature in the first week post-inoculation. The intradermal group had swelling with pus at the site of infection. Blood profile of the goats revealed significant decreased in haemoglobin for the intradermal and intranasal groups. Only the intradermal group showed significantly ($p<0.05$) high total WBC counts, with the increased neutrophils and monocyte concentrations. Generally, goats infected intradermally showed most severe clinical signs and haematology changes.

At the end of 30-day experimental period, all goats were sacrificed. *C. pseudotuberculosis* was re-isolated from most of the intradermally infected goats with 40% of the goats had the bacteria in the liver, 80% in prescapular and 40% in submandibular lymph nodes. Only 20% of goats in the intranasally infected group had the bacteria in the liver. No bacteria were isolated from any organ or lymph nodes from the oral and control goats. Abscessation was the most commonly observed gross lesions, particularly within the lymph nodes of infected goats. Other less common lesions included consolidation of lung lobes, congestion of kidneys and lymph nodes. Histopathological lesions scores revealed significantly ($p<0.05$) much severe overall lesions among goats exposed intradermally.

Following to the initial 30-day experimental trial, a chronic study was eventually conducted. Nine adult goats were similarly infected intradermally with $10^7$ cfu/mL of live *C. pseudotuberculosis* and were observed for 3 months. Similarly, all infected goats were less active in week 1 post-infection, developed swelling at the injection site with enlargement of submandibular lymph nodes. The haemoglobin, however, remained within normal value and decresed insignificantly ($p>0.05$) throughout the experimental period. Total white blood cell (WBC) counts were consistently high until day 39 post-infection due to the increased neutrophilic and monocytic counts. The serum IgG increased and exceeded the cut-off value on day 10 post-infection but most significant ($p<0.05$) increase was observed on day 14 post-infection before it gradually decreased until day 53 post-infection and approaching the cut-off value at the end of the 90-day experimental period.

Three goats were sacrificed by slaughtering monthly. *C. pseudotuberculosis* was successfully isolated from all lymph nodes with abscessation, and from the lungs of a goat that was sacrificed 2 months post-infection. Prescapular node abscessation was observed in 2 goats at 1 month post-inoculation, in all 3 goats at 2 and 3 months.There was also abscessation in the submandibular lymph node of a goat at 3 month post-inoculation.The lungs of infected goats showed thickening of interalveolar septa, mild to moderate congestion of the liver with inflammatory cells found scattered in between hepatocytes and presence of mild fatty degeneration of the hepatocytes. The kidneys showed congestion of blood vessels and presence ofurinary cast in the renal tubules.The affected lymph nodes showed typical abscess in which the diameter of the necrotic centre was significantly ($p<0.05$) larger with increase of time post-infection.These results show that the disease progressed with time after infection.

Currently, there is only one commercial vaccine for CLA in Malaysia. However, the efficacy was uncertain. Twenty-seven goats of different serological status were selected from a farm with endemic CLA. Group A consisted of 10 sero-positive goats, group B with 10 sero-negative goats while group C with 7 sero-negative goats that served as control-unvaccinated group. All goats of groups A and B were vaccinated using Glanvac 6$^{TM}$ vaccine twice at 1-month apart. One month after the second vaccination, all goats were challenged with $10^9$

cfu/mL of live *C. pseudotuberculosis.*The goats were observed for clinical signs and were killed a month post-infection. The bacterium was most frequently isolated from lymph nodes of goats of group A but the rate of isolation showed no significant ($p>0.05$) difference among all groups. Gross lesion was observed in the prescapular lymph nodes of all groups ($p>0.05$). The goats vaccinated with Glanvac 6$^{TM}$ either with sero-positive or sero-negative still developed signs and lesions of abscessation similar to the unvaccinated goats. Thus, the vaccine was unable to prevent goats from developing CLA.

**Keywords:** caseous lymphadenitis, *Corynebacterium pseudotuberculosis*, goats

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

**PATOGENESIS JANGKITAN *Corynebacterium pseudotuberculosis* DAN PERCUBAAN VAKSIN TERHADAP BENGKAK NODUS LIMFA PADA KAMBING**

Oleh

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*Corynebacterium pseudotuberculosis* adalah sejenis bakteria yang bertanggungjawab dalam menyebabkan penyakit bengkak nodus limfa pada kambing dan biri-biri.Penyakit ini tersebar meluas di seluruh dunia dan bakteria tersebut boleh berada di persekitaran selama beberapa bulan. Penghapusan penyakit ini sukar dilakukan dan ianya mudah merebak kepada haiwan-haiwan yang naïf. Penyebaran dan patologi penyakit in tidak difahami sepenuhnya. Penyelidikan ini dijalankan bagi mengenalpasti kaedah terlazim *C. pseudotuberculosis* menjangkiti kambing, kesan terhadap kambing secara klinikal dan patologikal selepas jangkitan serta tahap antibodi yang terbentuk dalam darah kambing, serta keberkesanan vaksin yang berada di pasaran ke atas sebaran dan kawalan penyakit ini pada kambing di Malaysia.

Dua puluh ekor kambing dewasa telah dipilih untuk penyelidikan ini dan dibahagikan kepada 4 kumpulan. Kambing-kambing tersebut telah dijangkiti dengan $10^7$ cfu/mL bakteria *C. Pseudotuberculosis* hidup melalui tiga kaedah. Kaedah-kaedah tersebut adalah; melalui kulit, saluran pernafasan dan mulut. Satu kumpulan kambing bertindak sebagai kawalan dan tidak dijangkiti bakteria. Kambing-kambing tersebut diperhatikan selama 30 hari untuk sebarang perubahan yang berkaitan dengan penyakit bengkak nodus limfa. Sepanjang masa itu, suhu badan dan sampel darah diambil mengikut selang masa yang ditetapkan. Pada minggu pertama jangkitan, semua kambing terjangkit kelihatan murung, kurang selera makan, dan suhu badan meningkat. Kambing-kambing yang dijangkiti pada kulit mempunyai bengkak yang mengandungi nanah pada kawasan terjangkit. Kambing-kambing terjangkit melalui kulit dan saluran pernafasan mengalami pengurangan dalam jumlah hemoglobin dalam darah. Hanya kambing terjangkit melalui kulit yg menunjukkan kenaikan bererti ($p<0.05$) dalam jumlah sel darah putih, dengan kenaikan jumlah sel neutrofil dan monosit. Kambing-kambing terjangkit melalui kulit menunjukkan tanda klinikal dan perubahan pada darah yang paling parah.

Selepas 30 hari jangkitan, semua kambing disembelih. Lesi-lesi kasar diperhatikan dan sampel organ-organ dalaman beserta nodus limfa diambil bagi pengasingan semula bacteria dan pemeriksaan histopatologi. Kebanyakkan pengasingan semula bacteria didapati dari kambing terjangkit melalui kulit. 40% kambing terdapat bacteria pada hati, 80% bacteria pada nodus limfa preskapular, dan 40% pada nodus limfa submandibular. Hanya 20% kambing terjangkit melalui saluran pernafasan mempunyai bacteria pada hati. Tiada pengasingan semula bakteria didapati dari kambing terjangkit melalui mulut dan kambing tidak terjangkit. Antara lesi kasar yang dapat dilihat adalah; pembentukan nanah pada nodus limfa, kemerahan pada paru-paru, buah pinggang dan nodus limfa. Lesi histopatologi menunjukkan kambing terjangkit melalui kulit mempunyai lesi yang lebih parah. Melalui penyelidikan ini, didapati nodus limfa yang paling banyak dijangkiti adalah nodus limfa preskapular. Jangkitan oleh *C. pseudotuberculosis* melalui kulit mempunyai lesi keseluruhan yang paling parah.

Berdasarkan keputusan penyelidikan di atas, 9 ekor kambing dewasa telah dipilih untuk penyelidikan seterusnya. Semua kambing dijangkiti melalui kulit dengan $10^7$ cfu/mL *C. pseudotuberculosis.* Kambing-kambing tersebut diperhatikan selama 3 bulan untuk sebarang tanda berkaitan bengkak nodus limfa. Suhu badan dan sampel darah diambil mengikut selang masa yang ditetapkan. Semua kambing terjangkit kelihatan tidak aktif pada minggu pertama jangkitan, mempunyai bengkak pada kawasan jangkitan, dan mengalami kenaikan suhu badan. Terdapat juga pembesaran pada nodus limfa submandibular sebesar 3 cm. Pembesaran tersebut dikesan pada seekor kambing pada minggu ke 8 jangkitan. Dalam penyelidikan ini, jumlah haemoglobin dalam darah adalah normal sepanjang 3 bulan penyelidikan, kecuali beberapa hari di penghujung penyelidikan. Jumlah sel darah putih dalam darah adalah tinggi selama 39 hari selepas jangkitan, tetapi kembali ke paras normal selepas itu. Jumlah neutrofil dan monosit dalam darah juga mengalami kenaikan yang sama. Paras IgG dalam serum kambing terjangkit juga di analisis. Paras IgG dalam serum meningkat dan melepasi titik potong pada hari kesepuluh selepas jangkitan. Paras IgG meningkat paling tinggi pada hari ke-14 selepas jangkitan. Bacaan ELISA mula menurun pada hari ke-53 selepas jangkitan dan menghampiri titik potong pada penghujung tempoh penyelidikan.

Tiga ekor kambing disembelih pada setiap bulan. Semasa post-mortem, lesi kasar diperhatikan dan sampel organ dalaman dan nodus limfa diambil untuk pengasingan semula bacteria dan pemeriksaan histopatologi. *C. pseudotuberculosis* berjaya diasingkan dari semua nodus limfa yang bernanah dan dari paru-paru seekor kambing yang disembelih pada bulan kedua selepas jangkitan. Terdapat nanah pada nodus limfa preskapular 2 ekor kambing yang disembelih pada bulan pertama selepas jangkitan. Pada bulan kedua selepas jangkitan, terdapat pendarahan pada paru-paru seekor kambing dan nanah pada nodus limfa preskapular semua kambing. Pada bulan ketiga selepas jangkitan, semua kambing terjangkit mempunyai organ dalaman yang kelihatan normal pada mata kasar. Tetapi, terdapat nanah pada nodus limfa preskapular pada semua kambing terjangkit dan nanah pada nodus limfa submandibular

dalam seekor kambing terjangkit. Pemeriksaan histologi menunjukkan penebalan pada septa interalveolar, kemerahan pada hati, kewujudan sel-sel radang pada hati, degenerasi lemak pada sel hati, kesesakan pada sel darah dalam buah pinggang, dan kast di dalam tubul buah pinggang. Nodus limfa yang bernanah menunjukkan keadaan nanah yang biasa. Nanah tersebut diukur dan didapati bahawa diameter bahagian tengah nanah tersebut meningkat dengan peningkatan masa selepas jangkitan. Keputusan ini menunjukkan penyakit ini bertambah teruk dengan peningkatan masa jangkitan.

Bengkak nodus limfa adalah penyakit yang penting dalam industri kambing di Malaysia, malahan di serata dunia. Oleh itu, pengawalan penyakit ini amat penting. Di Malaysia, hanya terdapat satu vaksin komersial terhadap penyakit ini. Oleh itu, keberkesanan vaksin ini harus dikaji. 27 ekor kambing dengan status serologi yang berbeza telah dipilih untuk penyelidikan ini. Kumpulan A mengandungi 10 ekor kambing sero-positif, kumpulan B mempunyai 10 sekor kambing sero-negatif dan kumpulan C terdiri daripada 7 ekor kambing sero-negatif yang bertindak sebagai kawalan. Semua kambing dalam kumpulan A dan B divaksin menggunakan vaksin komersial tersebut sebanyak 2 kali, dalam jarak 1 bulan. Sebulan selepas vaksinasi kedua, semua kambing dijangkitkan dengan $10^9$ cfu/ml *C. pseudotuberculosis.* Kambing-kambing tersebut diperhatikan untuk sebarang perubahan dan disembelih sebulan selepas jangkitan. Kebanyakkan pengasingan semula bakteria didapati dari kambing dalam kumpulan A. Tetapi, tiada perbezaan bererti ($p>0.05$) antara semua kumpulan kambing. Kebanyakkan lesi kasar didapati pada nodus limfa preskapular, dan tiada perbezaan bererti ($p>0.05$) antara semua kumpulan kambing. Lesi kasar menunjukkan bahawa kambing yang divaksin dengan Glanvac 6$^{TM}$ juga akan terjangkit dengan penyakit ini dan mempunyai nanah pada nodus linfa. Oleh itu, vaksin ini tidak berkesan sepenuhnya dalam menghalang penyakit ini kerana keberadaan penyakit ini tidak mempunyai perbezaan yang bererti ($p>0.05$) antara kambing yang divaksin dan kambing yang tidak divaksin.

**Kata kunci:** bengkak nodus limfa, *Corynebacterium pseudotuberculosis*, kambing

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I certify that a Thesis Examination Committee has met on 18 November 2016 to conduct the final examination of Nur Adza Rina binti Mohd Nordi on her thesis entitled "Pathogenesis of *Corynebacterium pseudotuberculosis* Infection and Vaccination Trial Against Caseous Lymphadenitis in Goats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| CLA: | caseous lymphadenitis |
| AGPT: | agar gel precipitation test |
| ELISA: | enzyme-linked immunosorbent assay |
| PBS: | phosphate buffered saline |
| BHI: | brain-heart infusion |
| CFU: | colony forming unit |
| SD: | standard deviation |
| CMN: | *Corynebacterium, Mycobacterium, Nocardia* |
| CBC: | complete blood count |
| WBC: | white blood cells |
| RBC: | red blood cells |
| PCV: | packed cells volume |
| PCR: | polymerase chain reaction |
| ANOVA: | analysis of variance |
| PLD: | phospholipase D |
| LN: | lymph node |
| IgG: | immunoglobulin G |
| bp: | base pairs |
| ºC: | degrees celcius |
| µL: | microlitre |
| g: | gram |
| p.i.: | post-infection |
| HE: | Haematoxylin and Eosin stain |
| rpm: | round per minute |

| | |
|---|---|
| APTT: | activated partial thromboplastin time |
| PT: | prothrombin time |
| BUN: | blood urea nitrogen |
| TP: | total protein |
| AST: | aspartate aminotransferase |
| ALP: | alkaline phosphatise |
| CK: | creatinine kinase |
| Alb: | albumin |
| GGT: | gamma-glutamyl transferase |
| A:G: | albumin and globulin ratio |
| OD: | optical density |

# CHAPTER 1

## INTRODUCTION

*Corynebacterium pseudotuberculosis* is the aetiological agent of a disease called caseous lymphadenitis (CLA) or “cheesy gland disease” that affects goats and sheep worldwide. It is a non-spore forming, facultative, intracellular Gram positive bacterium. In stained smears, the rods appear isolated and have pleomorphic form, from coccoids to filamentous rods that grouped in parallel cells or in a format similar to Chinese letters. In sheep blood agar incubated at 37°C, the organism appears as cream-colored colonies with a β-hemolysis zone at 48 h. It has a broad spectrum of hosts and causes clinical disease in sheep, goats, cattle, horses, pigs, deer, camels and laboratory animals, as well as in human (Moore *et al.*, 2010).

CLA is characterized by chronic abscess formation in superficial lymph nodes such as the submandibular, parotid, pre-scapular, subiliac, popliteal and supramammary lymph nodes. The internal lymph nodes are also affected such the mediastinal, bronchial and mesenteric lymph nodes. Occasionally, visceral organs like liver, lung and spleen might have the same abscessation (O’Reilly *et al.*, 2008).CLA has a severe economic impact on the sheep and goat industries due to reduction in wool, meat and milk production and condemnation of carcass and skins (Fontaine and Baird, 2008).Thus, it is important to understand more about the disease and to determine whether the current control and prevention measure is efficient in controlling the disease.

There are few postulated and confirmed routes of infection for the disease. It can occur through direct or indirect contact or through wounds that come into contact with pus from the sick animals. In naturally observed infections, the main portal of bacterial entry is generally accepted to be through the skin, normally as a result of the presence of minor wounds and abrasions (Collett *et al.*, 1994). A respiratory route for transfer of *C. pseudotuberculosis* has been postulated and some researchers suggest that animals with pulmonary lesions may present the major source of exposure to naive animals within a flock (Ellis *et al.*, 1987). In addition, head and neck lesions are thought to arise from bacterial entry via the oral cavity (Ashfaq and Campbell, 1979). To date, no study had been conducted to confirm the best route of transmission of the disease. Therefore, the most efficient route of infection should be determined to better understand the mechanism of the infection.

Vaccination against CLA is one of the ways to prevent infection by *C. psedotuberculosis*. Glanvac 6™ is a vaccine against several important small ruminant diseases that is currently available in Malaysia. It is a multicomponent adjuvanted vaccine containing *C. pseudotuberculosis* and

5 *Clostridium sp.*, which are *Clostridium perfringens* type D*, Clostridium tetani*, *Clostridium novyi* type B, *Clostridium septicum* and *Clostridium chauvoei*. It has been evaluated in many countries such as in Australia, Canada, and Saudi Arabia but not in Malaysia.

This study was conducted to evaluate *C. pseudotuberculosis* infection through different routes of infection. The viscerals organs and lymph nodes were examined for lesions and the commercial vaccine was assessed for efficiency against CLA in goats in Malaysia. The objectives of the present study are:

1. To determine the most efficient route of infection in producing CLA in goats.
2. To assess the clinical and pathological changes in goats following acute and chronic experimental infection by *C. pseudotuberculosis.*
3. To determine the efficiency of Glanvac 6$^{TM}$ vaccine against CLA in Malaysia.

Based on the objectives of the study, the hypotheses are:

1. The most efficient route of infection is via dermal route.
2. Following infection, lymph nodes abscessation is most frequently developed, with involvement of the visceral organs in which the severity increased with increasing time of infection.
3. The Glanvac 6$^{TM}$ vaccine is efficient in preventing caseous lymphadenitis among goatsin Malaysia.

## REFERENCES


Abdinasir, Y.O., Jesse, F.F.A., Saharee, A.A., (2012). Sero-prevalence of Caseous Lymphadenitis Evaluated by Agar Gel Precipitation Test among Small Ruminant Flocks in East Coast Economic Regions in Peninsular Malaysia. Journal of Animal and Veterinary Advances 11, 3474-3480.

Abdinasir, Y.O., Jesse, F.F.A., Saharee, A.A., Haron, A.W., Jasni, S., Rasedee, A., (2012). Haematological and Biochemical Alterations in Mice Following Experimental Infection with Whole Cell and Exotoxin (PLD) Extracted from *C. Pseudotuberculosis*. Journal of Animal and Veterinary Advances 11(24), 4660-4667.

Alloui, M.N., Kaba, J., Alloui, N., (2011). Prevalence and Risk Factors of CLA in Sheep and Goats of Batna Area (Algeria). Research Opinion in Animal and Veterinary Sciences 1(3), 162-164.

Al-Rawashdeh, O.F., Al-Qudah, K.M., (2000). Effect of Shearing on the Incidence of Caseous Lymphadenitis in Awassi Sheep in Jordan. Journal of Veterinary Medicine Series B 47, 287-293.

Annas, S., Zamri-Saad, M., Jesse, F.F., Zunita, Z., (2015). Comparative Clinicopathological Changes in Buffalo and Cattle Following Infection by *Pasteurella multocida* B: 2. Microbial Pathogenesis 88, 94-102.

Arsenault, J., Dubreuil, P., Girard, C., Simard, C., Bélanger, D., Maedi-Visna, (2003). Impact on Productivity in Quebec Sheep Flocks (Canada). Preventive Veterinary Medicine 59, 125–137.

Ashfaq, M.K., Campbell, S.G., (1979). A Survey of Caseous Lymphadenitis and Its Etiology in Goats in the United States. Veterinary Medicine, Small Animal Clinician 74, 1161-1165.

Ashfaq, M.K., Campbell, S.G., (1980). Experimentally induced caseous lymphadenitis in goats. American Journal of Veterinary Research 41(11), 1789-1792.

Bain, P.J., (2011). Liver, In: Duncan & Prasse's Veterinary Laboratory Medicine, Clinical Pathology, 211-229.

Baird, G.(2006). Treatment of Ovine Caseous Lymphadenitis. Veterinary Record 159, 500

Baird, G., Synge, B., Dercksend, (2004). Survey of Caseous Lymphadenitis Seroprevalence in British Terminal Sire Sheep Breeds. Veterinary Record 154, 505-506.

Baird, G.J., (2007). Caseous Lymphadenitis. In: Diseases of Sheep. 4th Edition, Blackwell Publishing, 306-311.

Baired, G.J., Fontaine, M.C., (2007). *Corynebacterium pseudotuberculosis* and Its Role in Ovine Caseous Lymphadenitis. Journal of Comparative Pathology 137, 179-210.

Barksdale, L., Linder, R., Sulea, I.T., Pollice, M., (1981). Phospholipase D Activity of *Corynebacterium pseudotuberculosis* (*Corynebacterium ovis*) and *Corynebacterium ulcerans*, a Distinctive Marker within the Genus *Corynebacterium*. Journal of Clinical Microbiology 13, 335-343.

Bastos, B.L., Dias Portela, R.W., Dorella, F.A., Ribeiro, D., Seyffert, N., (2012) *Corynebacterium pseudotuberculosis*: Immunological Responses in Animal Models and Zoonotic Potential. Journal of Clinical and Cellular Immunology S4:005.

Bastos, B.L., Dias Portela, R.W., Dorella, F.A., Ribeiro, D., Seyffert, N., Castro, T.L.P., Miyoshi, A., Oliveira, S.C., Meyer, R., Azevedo, V., (2012). *Corynebacterium pseudotuberculosis*: Immunological Responses in Animal Models and Zoonotic Potential. Journal of Clinical and Cellular Immunology S4:005.

Batey, R.G. (1985). Aspects of Pathogenesis in a Mice Model of Infection by *Corynebacterium pseudotuberculosis*. Australia Journal of Experimental Medical Science 64, 237-249.

Batey, R.G. (1986). Pathogenesis of Caseous Lymphadenitis in Sheep and Goats. Australian Veterinary Journal 63, 269-273

Biberstein, E.L., Knight, H.D., Jang, S., (1971). Two Biotypes of *Corynebacterium pseudotuberculosis.* Veterinary Record 89, 691-692.

Binns, S.H., Bairley, M., Green, L.E., (2002). Postal Survey of Ovine Caseous Lymphadenitis in the United Kingdom between 1990 and 1999. Veterinary Record 150: 263–268

Binns, S.H., Green, L.E., Bailey, M. (2007). Development and Validation of an ELISA to Detect Antibodies to *Corynebacterium pseudotuberculosis* in Ovine Sera. Veterinary Microbiology 123, 169-179.

Braverman, Y., Chizov-Ginzburg, A., Saran, A., (1999). The Role of Houseflies (*Musca domestica*) in Harbouring *Corynebacterium pseudotuberculosis* in Dairy Herds in Israel.Scientific and Technical Review of OIE (International Office of Epizootics) 18, 681–690.

Brown, C.C., Olander, H.J., (1987). Caseous Lymphadenitis of Goats and Sheep: a Review. Veterinary Bulletin 57, 1–11.

Brown, C.C., Olander, H.J., Biberstein, E.L.,Morse, S.M., (1986).Use of a Toxoid Vaccine to Protect Goats Against Intradermal Challenge Exposure to *Corynebacterium pseudotuberculosis*. American Journal of Veterinary Research 47, 1116–1119.

Burrel, D.H., (1980). A Haemolysis Inhibition Test for Detection of Antibody to *Corynebacterium ovis* Exotoxin. Researchin Veterinary Science 28 (2), 190-194.

Burtis, C.A., Ashwood, R.A., Bruns, E., (2000). Tiefz Fundamentals of Clinical Chemistry. Saunders. St. Louis.

Campbell, S.G., Ashfaq, M.K., Tashjian, J.J., (1982) Caseous Lymphadenitis in Goats in the USA. In: Proceedings 3rd International Conference on Goat Production and Disease. Tucson. Arizona 449–454

Cardenas, L., Clements, J.D., (1992). Oral Immunization Using Live Attenuated *Salmonella* spp. as Carriers of Foreign Antigens. Clinical Microbiology Reviews 5, 328-342.

Cetinkaya, B., Karahan, M., Atil, E., (2002). Identification of *Corynebacterium pseudotuberculosis* Isolates From Sheep and Goats by PCR. Veterinary Microbiology88, 75–83.

Chaplin, P.J., De Rose, R., Boyle, J.S., Mcwaters, P., (1999). Targeting Improves the Efficacy of a DNA Vaccine against *Corynebacterium pseudotuberculosis* in Sheep. Infection and Immunity67, 6434-6438

Collett, M.G., Bath, G.F., Cameron, C.M., (1994). *Corynebacterium pseudotuberculosis* Infections. In: Infectious Diseases of Livestock With Special Reference To Southern Africe, 2nd Edition, Coetzer,J., Thomson, G.R., Tustin,R.C., 2nd Edition, Oxford University Press, Cape Town, 1387-1395.

Connor, K.M., Quirie, M.M., Baird, G., Donachie, W., (2000). Characterization of United Kingdom Isolates of *Corynebacterium pseudotuberculosis* Using Pulsed-Field Gel Electrophoresis. Journal of Clinical Microbiology 38, 2633-2637.

Davis, H.L., Mancini, M., Michel, M.L., Whalen, R.G., (1996). DNA-Mediated Immunization to Hepatitis B Surface Antigen: Longevity of Primary Response and Effect of Boost. Vaccine14, 910-915.

Dercksen, D.P., Brinkhof, J.M.A., Dekker-Nooren, T., van Maanen,K., Bode, C.F., Baird, G., Kamp, E.M., (2000). A Comparison of Four Serological Tests for the Diagnosis of Caseous Lymphadenitis in Sheep and Goats. Veterinary Microbiology 75, 167–175.

Dorella, F.A., Pacheco, L.G., Oliveira, S.C., Miyoshi, A., Azavedo, V., (2006). *Corynebacterium pseudotuberculosis*: Microbiology, Biochemical Properties, Pathogenesis and Molecular Studies of Virulence. Veterinary Research37, 201-218.

Dorella, F.A., Pacheco, L.G., Seyffert, N., Portela, R.W., Meyer, R., (1998).*Corynebacterium pseudotuberculosis* For Use in Sheep. Journal of American Veterinary Medicine Association212, 1765–1768.

Dowling, A., Hodgson, J.C., Schock, A., Donachie, W., Eckersall, P.D., Mckendrick, I.J., (2002). Experimental Induction of Pneumonic Pasteurellosis in Calves by Intrtracheal Infection with *Pasteurella multocida* Biotype A: 3. Research in Veterinary Science 73, 37-44.

Egen, N.B., Cuevas, W.A., Mcnamara, P.J., Sammons, D.W., Humphreys, R., Songer, J.G., (1989). Purification of the Phopholipase D of *Corynebacterium pseudotuberculosis* by Recycling Isoelectric Focusing. American Journal of Veterinary Research 50, 1319-1322.

Eggleton, D.G., Doidge, C.V., Middleton, H.D., Minty, D.W., (1991). Immunization Against Ovine Caseous Lymphadenitis: Efficacy of the Monocomponent *Corynebacterium pseudotuberculosis* Toxoid Vaccine and Combined Clostridial-Corynebacterial Vaccines. Australian Veterinary Journal 68, 320-321.

Eggleton, D.G., Middleton, H.D., Doidge, C.V., Minty D.W., (1991). Immunization Against Ovine Caseous Lymphadenitis: Comparison of *Corynebacterium pseudotuberculosis* Vaccines With and Without Bacterial Cells. Australian Veterinary Journal 68, 317–319

Ellis, T.M., Sutherland, S.S., Wilkinson, F.C., (1987). The Role of *Corynebacterium pseudotuberculosis* Lung Lesions in the Transmission of This Bacterium to Other Sheep. Australian Veterinary Journal 64, 261-263.

Ferreira, R., Fonseca, L.S., Lilenbaum, W., (2002). Agar Gel Immunodiffusion Test (AGID) Evaluation for Detection of Bovine Paratuberculosis in Rio de Janeiro, Brazil. Letters in Applies Microbiology 35, 173-175.

Fontaine, M.C., Baird, G., Connor, K.M., (2006). Vaccination Confers Significant Protection of Sheep against Infection with a Virulent United Kingdom Strain of *Corynebacterium pseudotuberculosis*. Vaccine 24, 5986–5996.

Fontaine, M.C., Baird, G.J., (2008).CaseousLymphadenitis. Small Ruminant Research 76, 42–48

Goldberg, A.C., Lipsky, B.A., Plorde, J.J., (1981). Suppurative Granulomatous Lymphadenitis Caused by *Corynebacterium ovis (Pseudotuberculosis).*American Society of Clinical Pathologists 76, 486-490.

Hard, G.C., (1969). Electron Microscopic Examination of *Corynebacterium ovis*. Journal of Bacteriology 97(3), 1480-1485.

Hassan, N.A., Al-Humiany, A.A., Bahobail, A.S., Mansour, A.M.A., (2011). Bacteriological and Pathological Studies on Caseous Lymphadenitis in Sheep in Saudi Arabia. International Journal of Microbiological Research 2(1), 28-37.

Hawari, A.D. (2008). *Corynebacterium pseudotuberculosis* Infection (CLA) in Camels (*Camelus diomedarius*) in Jordon. American Journal of Animal and Veterinary Sciences 3(2), 68-72.

Hodgson, J.C., Dagleish, M.P., Gibbard, L., Bayne, C.W., Finlayson, J., Moon, G.M., Nath, M., (2013). Seven Strains of Mice as Potential Models of Bovine Pasteurellosis Following Intranasal Challenge with a Bovine Pneumonic Strain of *Pasteurella multocida* A: 3, Comparisons of Disease and Pathological Outcomes. Research in Veterinary Science 94, 634-640.

Hodgson, A.L., Carter, K., Tacedjian, M., Krywult, J., Coener, L.A., Mccoll, M., Cameron, A., (1999). Efficacy of an Ovine Caseous Lymphadenitis Vaccine Formulated Using a Genetically Inactive Form of the *Corynebacterium pseudotuberculosis* Phospholipase D. Vaccine 17, 802-808.

Hodgson, A.L., Tachedjian, M., Corner, L.A., Radford, A.J., (1994). Protection of Sheep against Caseous Lymphadenitis by Use of a Single Oral Dose of Live Recombinant *Corynebacterium pseudotuberculosis*. Infection and Immunity 62, 5275-5280.

Ibtisam, M.A. (2008). Some Clinicopathological and Pathological Studies of *Corynebacterium ovis* Infection in Sheep. Egypt Journal of Comparative Pathology of Clinical Pathology 21(1), 327-343.

Ismail, A.A., Hamid, Y.M.A., (1972). Studies on the Effect of Some Chemical Disinfectants Used in Veterinary Practice in *Corynebacterium ovis*. Journal of Egyptian Veterinary Medicine Association 32, 195–202.

Jesse, F.F.A., Randolf, P.S.S., Saharee, A.A., Wahid, A.H., Zamri-Saad, M., Jasni, S., Omar, A.R., Adamu, L., Abdinasir, Y.O., (2013). Clinico-pathological response of mice following oral route infection of *Corynebacterium pseudotuberculosis*. Journal of Agriculture and Veterinary Science 2, 38-42.

Jiskoot, W., Kersten, G.F.A., Beuvery, E.C., (2002). Vaccine. In: Crommelin, D.J.A., Sindelar, R.D., Pharmaceutical Biotechnology – An introduction for Pharmacists and Pharmaceutical Scientists, 2nd Edition. London: Taylor and Francis Group, 259–282.

Johnson, E.H., Vidal, C.E.S., Santa Rosa, J., Kass, P.H., (1993). Observations on Goats Experimentally Infected with *Corynebacterium pseudotuberculosis*. Small Ruminant Research 12, 357-369.

Jolly, R.D., (1966). Some Observations on Surface Lipids of Virulent and Attenuated Strains of *Corynebacterium ovis*. Journal of Applied Bacteriology 29, 189-196.

Jolly, R.D.,(1965). The Pathogenesis of Experimental *Corynebacterium ovis* Infection in Mice. New Zealand Veterinary Journal, 13, 141-142.

Jones, D., Collins, M.D., (1986). Irregular, Nonsporing Gram-Positive Rods. In: Sneath, P.H.A. Bergey's Manual of Systematic Bacteriology, 2nd edition. Baltimore: Williams and Wilkins, 1261–1282.

Jubb, K.V.F., Kennedy, P.C., Palmer, N., (1998). Pathology of Domestic Animals, 3rd Edition Academic Press, Orlando, FA.

Keslin, M.H., Mccoy, E.L., Mccusker, J.J., Lutch, J.S., (1979). *Corynebacterium pseudotuberculosis.* A New Cause of Infectious and Eosinophilic Pneumonia. American Journal of Medicine, 67, 228-231.

Komala, T.S., Ramlan, M., Yeoh, N.N., Surayani, A.R., Sharifah Hamidah, S.M., (2008).A Survey of Caseous Lymphadenitis in Small Ruminant FarmsFrom Two Districts in Perak, Malaysia – Kinta and Hilir Perak.Tropical Biomedicine25(3), 196–201.

Kuria, J.K.N., Mbuthia, P.G., Kang'ethe, E.K., Wahome, R.G., (2001). Caseous Lymphadenitis in Goats: The Pathogenesis, Incubation Period and Serological Response after Experimental Infection. Veterinary Research Communication 25, 89-97.

Liu**,** D.T.L, Chan**,** W.M.,Fan**,** D.S.P,Lam, D.S.C, (2005).An Infected Hydrogel Buckle with *Corynebacterium pseudotuberculosis* British Journal of Ophthalmology, 89:245-246

Lopez, J.F., Wonc, F.M., Quesada, J., (1966). *Corynebacterium pseudotuberculosis* First Case of Human Infection. American Journal of Clinical Pathology 46, 562.

Mahmood, Z.K.H., F.F. Jesse, A.A. Saharee, S. Jasni, R. Yusoff and H. Wahid (2015). Clinico-Pathological Changes in Goats Challenged with *Corynebacterium pseudotuberculosis* and its Exotoxin (PLD). American Journal of Animal and Veterinary Sciences 10 (3): 112.132

Mahmood, Z.K.H., F.F. Jesse, A.A. Saharee, S. Jasni, R. Yusoff and H. Wahid (2015). Assessment of Blood Changes Post-challenge with *Corynebacterium pseudotuberculosis* and Its Exotoxin (Phospholipase D): AComprehensive Study in Goat. Veterinary World 8(9): 1105-1117.

Maki, L.R., Shen, S.H., Bergstrom, R.C., Stetzenbach, L.D., (1985).Diagnosis of *Corynebacterium pseudotuberculosis* Infections inSheep, Using an Enzyme-Linked Immunosorbent Assay. American Journal of Veterinary Research 46 (1), 212–214.

Malaysian Veterinary Protocol: Caseous Lymphadenitis, (2011). PVM 3(13):1/2011

Menzies, P.I., Hwang, Y.T., Prescott, J.F., (2004). Comparison of an Interferon-Γ To a Phospholipase D Enzyme-Linked Immunosorbent Assay for Diagnosis of *Corynebacterium pseudotuberculosis* Infection in Experimentally Infected Goats. VeterinaryMicrobiology100, 129–137.

Menzies, P.I., Muckle, C.A., Brogden, K.A., Robinson, L., (1991). A Field Trial to Evaluate a Whole Cell Vaccine for the Prevention of Caseous Lymphadenitis in Sheep and Goat Flocks. Canada Journal of Veterinary Research 55, 362-366.

Menzies, P.I., Muckle, C.A., Hwang, Y.T., Songer, J.G., (1994). Evaluation of an Enzyme Linked Immunosorbent Assay Usingan *Escherichia coli* Recombinant Phospholipase D Antigen for theDiagnosis of *Corynebacterium pseudotuberculosis* Infection. Small Ruminant Research 13, 193–198.

Mills, A.E.,Mitchell, R.D.,Lim, E.K., (1997). *Corynebacterium pseudotuberculosis* is a Cause of Human Necrotising Granulomatous Lymphadenitis. Pathology 29(2), 231-233.

Miyoshi, A., Azevedo, V., (2009). Antigens of *Corynebacterium pseudotuberculosis* and Prospects for Vaccine Development. Expert Review Vaccines8(2), 205–213.

Moller, K., Agerholm, J.S., Ahrens, P.,(2000). Abscess Disease, Caseous Lymphadenitis and Pulmonary Adenomatosis in Imported Sheep. Journal of Veterinary Medicine B: Infectious Diseases and Veteterinery Public Health47, 55-62.

Moore, R., Miyoshi, A., Pacheco, L.G.C., Seyffert, N., Azevedo, V., (2010). Corynebacterium and Arcanobacterium. In: Pathogenesis of Bacterial Infection in Animals. 1st Edition, Blackwell Publishing, 133-147.

Muckle, C.A., Gyles, C.L., (1982). Characterization of Strains of *Corynebacterium pseudotuberculosis*. Canada Journal of Comparative Medicine 46, 206-208.

Nguyen, D., Diamond, L., (2000). Neutrophilia Pattern in: Diagnostic Haematology, a Pattern Approach. 1st Edition, Butterworth-Heinemann, London.

O'Reilly, K.M., Green, L.E., Malone, F.E., Medley, G.F., (2008). Parameter Estimation and Simulations of a Mathematical Model of *Corynebacterium pseudotuberculosis* Transmission in Sheep. Preventive Veterinary Medicine83, 242–259.

Okwor, E.C., Eze, D.C., Okonkwo, K.E., Ibu, J.O., (2011). Comparative Evaluation of Agar Gel Precipitation Test (AGPT) and Indirect Haemaagglutination Test (IHA) for the Detection of Antibodies against Infectious Bursal Disease (IBD) Virus in Village Chickens. African Journal of Biotechnology 10(71), 16024-16027.

Othman, A.M, Jesse, F.F.A., Adza- Rina, M.N., Ilyasu, Y., Zamri-Saad, M., Wahid, A.H., Saharee, A.A. and Mohd-Azmi. M.L. (2014). Haematological, Biochemical and Serum Electrolyte Changes in Non-Pregnant Boer Does Inoculated With*Corynebacterium pseudotuberculosis* Via Various Routes. Journal of Agriculture and Veterinary Science 7, 05-08

Othman, A.M., Abba, Y., Jesse, F.F.A., Ilyasu, Y.M., Saharee A.A., Haron, A.W., Zamri-Saad, M., Lila, M.A.M., (2016). Reproductive Pathological Changes Associated with Experimental Subchronic *Corynebacterium pseudotuberculosis* Infection in Non-Pregnant Boer Does. Journal of Pathogens. Hindawi Publishing Corporation.

Paton, M.W., Walker, S.B., Rose, I.R., Watt, G.F., (2003). Prevalence of Caseous Lymphadenitis and Usage of Caseous Lymphadenitis Vaccines in Sheep Flocks. Australia Veterinary Journal 81, 91-95

Paule, J.A., Azevedo, V., Regis, L.F., Carminati, R., Bahia, C.R., Vale, V.L.C., Moura-Costa L.F., Freire, S.M., Nascimento, I., Schaer, R., Goes, A.M., Meyer, R., (2003). Experimental *Corynebacterium pseudotuberculosis* Infection in Goats: Kinetics of IgG and Interferon-ɣ Production, IgG Avidity and Antigen Recognition by Western Blotting. Veterinary Immunology and Immunopathology 96, 129-139.

Peel, M.M., Palmer, G.G., Stacpoole, A.M., Kerr, T.G., (1997). Human Lymphadenitis Due to *Corynebacterium pseudotuberculosis*: Report of Ten Cases from Australia and Review. Clinical Infectious Diseases 24, 185-191.

Pekelder, J.J., (2003). Caseous Lymphadenitis. In: Martin, W.B., Aitken, I.D., Diseases of Sheep. 3rd Edition, Blackwell Science, Oxford.

Pepin, M., Fontaine, J.J., Pardon, P., Marly, J., Parody, A.L., (1991). Histopathology of the Early Phase during Experimental *Corynebacterium pseudotuberculosis* Infection in Lambs. Veterinary Microbiology 29, 123-134.

Pepin, M., Pardon, P., Lantier, F., Marly, J., Levieux, D., Lamand, M., (1990). Experimental *Corynebacterium pseudotuberculosis* Infection in Lambs: Kinetics of Bacterial Dissemination and Inflammation. Veterinary Microbiology 26, 381-392.

Pepin, M., Paton, M., Hodgson, A.L, (1994). Pathogenesis and Epidemiology of *Corynebacterium pseudotuberculosis* Infection in Sheep. Current Topics in Veterinary Research 1, 63-82.

Pepin, M., Seow, H.F., Corner, L., Rothel, J.S., Hodgson, A.L., (1997). Cytokine Gene Expression in Sheep Following Experimental Infection with Various Strains of *Corynebacterium pseudotuberculosis* differing in Virulence. Veterinary Research 28, 149-163.

Pfizer Australia Pty Ltd (2010). Glanvac™ 6 pamphlet, Pfizer Animal Health.

Pinder, A.G., Rogers, S.C., Morris, K., James, P.E., (2009). Haemoglobin Saturation Controls the Red Blood Cells Mediated Hypoxic Vasorelaxation, In: Oxygen Transport in Tissue. Springer U.S, 13-20.

Quinn, P.J., Carter, M.E., Markey, B., Carter, G.R., (1994) *Corynebacterium* species and *Rhodococcus equi* In: Clinical Veterinary Microbiology. Wolfe PublishingCompany, London.

Radostits, N.M., Gay, C.C., Hinchcliff, W.K., Constable, P.D., (2007). Veterinary Medicine: A Textbook of the Disease of Cattle, Horses, Sheep, Pigs and Goats. 10th Edition. Saunders Publisher, USA, 314-325.

Radostits, O.M., Gay, C.C., Blood, D.C., Hinchcliff, K.W., (2000). Caseous Lymphadenitis in Sheep and Goats. Veterinary Medicine, 9th Edition, W.B. Saunders, London, 727-730.

Rhyan. J.C., Saari, D.A., Williams, E.S., (1992). Gross and Microscopic Lesions of Naturally Occurring Tuberculosis in a Captive Herd of Wapiti (*Cervus elaphus nelson*) in Colorado. Journal of Veterinary Diagnosis and Investigation 4, 428-433.

Saragea, A., Maximescu, P., Meitert, E., Stuparu, I., (1966). Incidence and Geographical Distribution of Phage Types of *Corynebacterium diphtheriae* in the Dynamics of the Epidemic Process of Diphtheria in the Rumanian Socialist Republic. Microbiology, Parasitology and Epidemiology11, 351-362

Schreuder, B.E., Ter Laak E.A., Dercksen, D.P., (1994). Eradication of Caseous Lymphadenitis in Sheep with the Help of a Newly Developed ELISA Technique. Veterinary Record135, 174-176.

Senturk, S., Temizel, M., (2006). Clinical Efficacy of Rifamycin SV Combined with Oxytetracycline in the Treatment of Caseous Lymphadenitis in Sheep. Veterinary Record 159, 216–217

Serres E., Hehenberger E., Allen A.L., (2011). Multiple Pyogranulomas in a Katahdin Ewe. Canadian Veterinary Journal 52, 555-560

Seyffert, N., Guimaraes, A.S., Pacheco, L.G.C., Portela, R.W., Bastos, B.L., Dorella, F.A., Heinemann, M.B., Lage, A.P., Gouveia, A.M.G., Meyer, R., Miyoshi, A., Azevedo, V.,(2010). High Seroprevalence of Caseous Lymphadenitis in Brazilian Goat Herds Revealed by *Corynebacterium*

*pseudotuberculosis* Secreted Protein-Based ELISA. Research in Veterinary Science 88, 50-55

Smith, M.C., Sherman, D., (1994). Caseous Lymphadenitis. Goat Medicine, 1st Edition, Lea and Febier, Iowa.

Songer, J.G. (1997). Bacterial Phospholipases and Their Role in Virulence. Trendsin Microbiology 5, 156-160.

Songer, J.G., Beckenbach, K., Marshall, M.M., Olson, G.B., Kelly, L., (1988). Biochemical and Genetic Characterization of *Corynebacterium peudotuberculosis*. American Journal of Veterinary Research 49, 221-226.

Stoops, S.G., Renshaw, H.W., Thilsted, J.P., (1984). Ovine Caseous Lymphadenitis: Disease Prevalence, Lesion Distribution and Thoracic Menifestations in a Population of Mature Culled Sheep from Western United States. American Journal of Veteterinary Research 45, 557-561.

Sutherland, S.S., Eillis, T.M., Mercy, A.R.,Paton, M.W. & Middleton, H., (1987). Evaluation of an Enzyme-Linked Immunosorbent Assay for the Detection of *Corynebacterium pseudotuberculosis* Infection in Sheep. Australian Veterinary Journal 64 (9), 263-266.

Tashjian, J.J., Campbell, S.G., (1983). Interaction between Caprine Macrophages and *Corynebacterium pseudotuberculosis*: An Electron Microscopic Study. American Journal of Veterinary Research 44, 690-693.

Ter Laak, E.A., Bosch, J., Bijl, G.C., Screuder, B.E.C., (1992). DoubleAntibody Sandwich Enzyme-Linked Immunosorbent Assay andImmunoblot Analysis Used for Control of Caseous Lymphadenitis in Goats and Sheep. American Journal of Veterinary Research 53 (7), 1125–1132.

Toshach, S., Valentine, A., Sigurdson, S., (1977). Bacteriophage Typing of *Corynebacterium diphtheriae*. Jornal of Infectious Diseases 136, 655-660

Tunkel A.R., (2012). Fever, In: MSD Manual Professional Version. Merck & Co., Kenilworth, New Jersey, United States of America.

Ural, K., Alic, D., Haydardedeoglu, A.E., (2008). *Corynebacterium pseudotuberculosis* Infection in Saanen×Kilis Crossbred (White) Goats in Ankara, Turkey and Effective Kanamycin Treatment: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. Small Ruminant Research77, 84–88

Wagner, K.S., White, J.M., Crowcroft, N.S., Mann, G., Efstratiou, A., (2010). Diphtheriain the United Kingdom, 1986-2008: the Increasing Role of *Corynebacteriumulcerans*. Epidemiology and Infection 138, 1519-1530.

Walker, J., Jackson, H., Brandon, M.R., Meeusen, E., (1991). Lymphocyte Subpopulations in Pyogranulomas of Caseous Lymphadenitis. Clinical and Experimental Immunology 86(1), 13-18.

Wawrzkiewicz, J., Dziedzic, B., Koziol, T., (1989). Sensitivity and Specificity of a Modified Agar Gel Precipitation Test and Its Application to the Diagnosis of Enzootic Bovine Leukosis. Acta Virologica 33(2), 143-50.

West, D.M., Bruere, A.N., Ridler, A.L., (2002). Caseous Lymphadenitis. In: The Sheep: Health, Disease and Production. Foundation for Veterinary Continuing Education, Massey University, New Zealand.

Williamson, L.H., (2001). Caseous Lymphadenitis in Small Ruminants. Veterinary Clinics of North America: Food Animals Practice 17, 359-371.

Wolf, C., (2007). North America. In: Diseases of Sheep. 4th Edition, Blackwell Publishing, 511.

Yeruham, I., Braverman, Y., Shpigel, N.Y., (1996). Mastitis in Dairy Cattle Caused by *Corynebacterium pseudotuberculosis* and the Feasibility of Transmission by Houseflies. Veterinary Quarterly18, 87–89.

Zavoshti, F.R., Khoojine, A.B.S., Helan, J.A., Hassanzadeh, B., Heydari, A.A., (2012). Frequency of caseous lymphadenitis (CLA) in Sheep Slaughtered in an Abbatoir in Tabriz: Comparison of Bacterial Culture and Pathological Study. Comparative Clinical Pathology 21, 667-671.